ANTIBIOTIC STEWARDSHIP

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DEFINITION OF ANTIMICROBIAL STEWARDSHIP

The optimal selection, dose and duration of an antimicrobial that results in the best clinical outcome with minimal toxicity to the patient,

and minimal impact on subsequent development of resistance.

Owens RC et al. Diagn Microbiol Infect Dis. 2007;57(3 suppl):77S-83S.
OVERVIEW

• What is antimicrobial resistance and what threat does it pose?

• What is the WHO action plan for antibiotic stewardship and South Africa’s commitment?

• Antibiotic stewardship programme at Tygerberg hospital
OVERVIEW

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MEAT + DRUGS = SUPERBUGS

80% of antibiotics in the U.S. are used on factory farms.

Risk assessment

Control resistance emergence in the environment

Control antibiotic resistance dissemination (management and policy)

Control resistance transmission to humans

Environment

Define resistance in environmental strains

Standardize testing in environmental samples

Clinic

Understand the relationship between the environmental and clinical antibiotic resistance

Nature Reviews | Microbiology

www.foodconnect.com
ANTIBIOTIC RESISTANCE
A type of drug resistance which renders the antibiotic ineffective in killing or controlling the bacterial growth.

WHY IS ANTIBIOTIC RESISTANCE A PROBLEM?
MORE THAN 40 MILLION Antibiotic prescriptions in 2011 were unnecessary!

No new major antibiotic has been developed in the last 30 years.

NEARLY 50% OF U.S. MEAT IS CONTAMINATED WITH BACTERIA THAT IS RESISTANT TO VARIOUS ANTIBIOTICS.

ADULTS 60% ANTIBIOTICS PRESCRIBED ARE NOT NEEDED.
CHILDREN 30% ANTIBIOTICS PRESCRIBED ARE NOT NEEDED.

WHAT THE STATISTICS REVEAL?
ONLY 10 PERCENT ADULTS are prescribed the correct antibiotic for Strep infections.

ONLY ZERO PERCENT CORRECT PRESCRIBING RATE for acute bronchitis.

OVER FOUR PERCENT INCREASE in antibiotic prescription rates in last 14 years.

PERCENTAGE OF ANTIBIOTICS CURRENTLY USED IN THE FOOD CHAIN.
76% 24%

Only 24% of antibiotics used in the U.S. are for humans.

76% OF ANTIBIOTICS IN THE U.S. ARE USED FOR LIVESTOCK ONLY. Out of this, only 6% accounts for therapeutic purpose!
CONSEQUENCES OF INAPPROPRIATE THERAPY

- Excessive use
- Inappropriate ABO administration
- Suboptimal dosing

Collateral damage

Selection of drug resistant organisms
Infection with multi-drug resistant pathogens
MULTIDRUG-RESISTANT ACINETOBACTER

7,300
MULTIDRUG-RESISTANT ACINETOBACTER INFECTIONS

500
DEATHS FROM MULTIDRUG-RESISTANT ACINETOBACTER INFECTIONS

12,000
ACINETOBACTER INFECTIONS PER YEAR

THREAT LEVEL: SERIOUS

This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow.

NO LONGER CURE RESISTANT ACINETOBACTER INFECTIONS

VANCOMYCIN-RESISTANT ENTEROCOCCUS (VRE)

20,000
DRUG-RESISTANT ENTEROCOCCUS INFECTIONS

1,300
DEATHS FROM DRUG-RESISTANT ENTEROCOCCUS INFECTIONS

66,000
ENTEROCOCCUS INFECTIONS PER YEAR

THREAT LEVEL: SERIOUS

Some enterococcus strains are resistant to vancomycin, leaving few or no treatment options.

METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

80,461
SEVERE MRSA INFECTIONS PER YEAR

11,285
DEATHS FROM MRSA PER YEAR

THREAT LEVEL: SERIOUS

Staphylococci are a leading cause of healthcare-associated infections.

FLUCONAZOLE-RESISTANT CANDIDA

3,400
FLUCONAZOLE-RESISTANT CANDIDA INFECTIONS

220
DEATHS

46,000
CANDIDA INFECTIONS PER YEAR

THREAT LEVEL: SERIOUS

This fungus is a serious concern and requires prompt and sustained action to ensure the problem does not grow.
But what if there were no treatment options left?

A return to the pre-antibiotic era...
A PERFECT STORM

As bacterial infections grow more resistant to antibiotics, companies are pulling out of antibiotics research and fewer new antibiotics are being approved.

**Antibiotic-resistant (%)**

*Proportion of clinical isolates that are resistant to antibiotic: MRSA, methicillin-resistant Staphylococcus aureus. VRE, vancomycin-resistant Enterococcus. FQRP, fluoroquinolone-resistant Pseudomonas aeruginosa.*
HOW RESISTANCE HAPPENS

• Simply using antibiotics creates resistance
MAJOR MECHANISMS OF RESISTANCE

• Change the antibiotic binding site
• Destroy antibiotic (β-lactamases)
• Don’t let the antibiotic in or pump the antibiotic out
Estimates of Burden of Antibacterial Resistance

**European Union**  
*population 500m*  
25,000 deaths per year  
2.5m extra hospital days  
Overall societal costs  
(€ 900 million, hosp. days)  
Approx. €1.5 billion per year  
Source: ECDC 2007

**Thailand**  
*population 70m*  
>38,000 deaths  
>3.2m hospital days  
Overall societal costs  
US$ 84.6–202.8 mill. direct  
>US$1.3 billion indirect  
Source: Pumart et al 2012

**United States**  
*population 300m*  
>23,000 deaths  
>2.0m illnesses  
Overall societal costs  
Up to $20 billion direct  
Up to $35 billion indirect  
Source: US CDC 2013

Global information is insufficient to show complete disease burden impact and costs
Risk of Death is Higher in Patients Infected with Resistant Strains

<table>
<thead>
<tr>
<th>Outcome (number of studies included)</th>
<th>Deaths (%)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resistant</td>
<td>Not resistant</td>
<td>RR (95% CI)</td>
<td></td>
</tr>
<tr>
<td><strong>Escherichia coli</strong> resistant to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3^rd gen. cephalosporins</td>
<td>Bacterium attributable mortality (n=4)</td>
<td>23.6</td>
<td>12.6</td>
<td>2.02 (1.41 to 2.90)</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Bacterium attributable mortality (n=1)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae</strong> resistant to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3^rd gen. cephalosporins</td>
<td>Bacterium attributable mortality (n=4)</td>
<td>20</td>
<td>10.1</td>
<td>1.93 (1.13 to 3.31)</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Bacterium attributable mortality (n=1)</td>
<td>27</td>
<td>13.6</td>
<td>1.98 (0.61 to 6.43)</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong> resistant to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methicillin (MRSA)</td>
<td>Bacterium attributable mortality (n=46)</td>
<td>26.3</td>
<td>16.9</td>
<td>1.64 (1.43 to 1.87)</td>
</tr>
</tbody>
</table>
One child is dying every five minutes because the antibiotic given is ineffective

Neonatal sepsis in five countries in South Asia
( India, Pakistan, Afghanistan, Nepal, Bangladesh),

Zulfiqar Bhutta ReAct conference, 2010
http://www.reactgroup.org/resource-centre/react-presentations/need-for-effective-antibiotics.html
The Burden of Antibiotic Resistance in Indian Neonates

1 million Indian children die in the **first 4 weeks** of life each year...

Of these deaths, **190,000** are caused by sepsis, a bacterial infection that overtakes the bloodstream.

**58,319**, or **just over 30%**, of neonatal sepsis deaths are attributable to antibiotic resistance.

Sources:

Images: Stock photo, Florida Center for Instructional Technology

www.cddep.org
OVERVIEW

• What is antimicrobial resistance and what threat does it pose?

• What is the WHO action plan for antibiotic stewardship and South Africa’s commitment?

• Antibiotic stewardship programme at Tygerberg hospital
WHO – GLOBAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE - 2015

FIVE STRATEGIC OBJECTIVES

• To improve awareness and understanding of antimicrobial resistance
• To strengthen the knowledge and evidence base through surveillance and research
• To reduce the incidence of infection (IPC mechanisms)
• To optimize the use if antimicrobial medicines
• To develop the economic case for sustainable investment
WHO SHOULD BE INVOLVED?
ANTIBIOTIC STEWARDSHIP TEAM

- Pharmacy
- Infection Control
- HCF managers
- Medical Doctors
- Data manager
- Microbiology
TARGETS FOR ANTIMICROBIAL STEWARDSHIP INTERVENTIONS

Susceptible Pathogen

Prevent, Transmission

Antimicrobial Resistance

Prevent Infection

Infection

Effective Diagnosis & Treatment

Optimize Use

Antimicrobial Use

1. Break the chain
2. Access the experts
3. Target the pathogen
4. Get the catheters out
5. Vaccinate
6. Use local data
7. Treat infection, not colonization
8. Treat infection, not contamination
9. Know when to say “no” to vancomycin
10. Stop treatment when cured
11. Isolate the pathogen

Prevent Transmission

Diagnose & Treat Effectively

Prevent Infections

Use Antimicrobials Wisely

TV Rao
IMPLEMENTATION OF ANTIBIOTIC STEWARDSHIP IN SOUTH AFRICA: 2014-2019
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ANTIMICROBIAL STEWARDSHIP PLAN AT TBH

1. Selective reporting from NHLS microbiology – alert organisms

2. Antibiotic stewardship ward rounds and antimicrobial restrictions and prescribing guidelines

3. Dedicated antibiotic prescription charts

4. Expansion of the BCA campaign and IPC programme
Gram negative pathogens predominate (neonatal HA-BSI at Tygerberg Hospital)

Top 10 BSI pathogens (n= 717; 93% of total pathogens)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>K. pneumoniae</td>
<td>30</td>
</tr>
<tr>
<td>S. marcescens</td>
<td>11</td>
</tr>
<tr>
<td>A. baumannii</td>
<td>9</td>
</tr>
<tr>
<td>E. coli</td>
<td>7</td>
</tr>
<tr>
<td>E. cloacae</td>
<td>2</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>2</td>
</tr>
<tr>
<td>S. aureus</td>
<td>14</td>
</tr>
<tr>
<td>Enterococcus spp</td>
<td>11</td>
</tr>
<tr>
<td>Group B streptococci</td>
<td>5</td>
</tr>
<tr>
<td>Candida spp</td>
<td>4</td>
</tr>
</tbody>
</table>

Gram negatives (65%)  Gram positives (31%)  Fungi (4%)
Neonatal HA-BSI: high-level antimicrobial resistance

Prevalence of selected antimicrobial resistance phenotypes

- Methicillin resistant S. aureus: [VALUE]%
- MDR A. baumannii: [VALUE]%
- ESBL K. pneumoniae: [VALUE]%
- ESBL E. coli: [VALUE]%
- Fluconazole resistant Candida spp: [VALUE]%

Neonatal HA-BSI isolates (n = 796; 2009-2013)
In vitro susceptibility to empiric antibiotic regimens

<table>
<thead>
<tr>
<th>Antibiotic Regimen</th>
<th>Overall % Susceptible in Vitro</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEN+AMIK</td>
<td>[VALUE]%</td>
</tr>
<tr>
<td>PIPTAZ+AMIK</td>
<td>[VALUE]%</td>
</tr>
<tr>
<td>MERO</td>
<td>[VALUE]%</td>
</tr>
<tr>
<td>MERO+AMIK</td>
<td>[VALUE]%</td>
</tr>
<tr>
<td>MERO+VANCO</td>
<td>[VALUE]%</td>
</tr>
</tbody>
</table>

Neonatal HA-BSI episodes (n = 717; 2009-2013)
TCH NEONATAL SEPSIS ALGORITHM

* stable neonate = suspicion of sepsis, but no major clinical deterioration
* unstable neonate = new requirement for nCPAP/ventilatory or inotropic support/shocked neonate
# Assumes blood culture/s, urine and CSF sent as indicated clinically. Inoculate at least 1-2ml blood into culture bottle to increase yield.
For culture-confirmed sepsis, most pathogens require 7 days therapy only (if unsure, discuss with microbiology or ID teams)

< 72 hours

<table>
<thead>
<tr>
<th>Nechote (days of life/hospitalisation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 72 hours</td>
</tr>
<tr>
<td>Nechatal wards (stable*)</td>
</tr>
<tr>
<td>Option 1: Ampicillin + Gentamicin</td>
</tr>
<tr>
<td>Option 2: Cefotaxime + Ampicillin</td>
</tr>
<tr>
<td>(if suspected meningitis)</td>
</tr>
<tr>
<td>If BC and CRP negative @ 48 hours stop IV AB</td>
</tr>
</tbody>
</table>

> 72 hours

<table>
<thead>
<tr>
<th>Nechatal wards and NICU (unstable**)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 72 hours</td>
</tr>
<tr>
<td>Option 1: Meropenem ± Colistin</td>
</tr>
<tr>
<td>(discuss with consultant)</td>
</tr>
<tr>
<td>Option 2: Meropenem (if suspected meningitis)</td>
</tr>
<tr>
<td>Consider adding Vancomycin</td>
</tr>
<tr>
<td>(if recent central lines or phlebitis)</td>
</tr>
<tr>
<td>Consider adding Fluconazole</td>
</tr>
<tr>
<td>(if further deterioration)</td>
</tr>
<tr>
<td>If BC and CRP negative @ 48 hours consider stopping IV AB OR complete 5 days therapy</td>
</tr>
</tbody>
</table>
WEEKLY ANTIBIOTIC STEWARDSHIP WARD ROUNDS
# DEDICATED ANTIBIOTIC STEWARDSHIP PRESCRIPTION CHARTS

## Tygerberg Hospital Antibiotic Stewardship Programme

### Antibiotic Prescription Chart

<table>
<thead>
<tr>
<th>Patient Label</th>
<th>Weight</th>
<th>Allergies</th>
<th>eGFR</th>
</tr>
</thead>
</table>

### Infection Episode 1

- **Diagnosis**
  - [ ] Pneumonia
  - [ ] UTI
  - [ ] Meningitis
  - [ ] Line infection
  - [ ] Cellulitis
  - [ ] Intra-abdominal infection
  - [ ] Other

- **Source**
  - [ ] Community acquired
  - [ ] Hospital acquired

- **Indication**
  - [P] Prophylactic
  - [E] Empirical
  - [D] Definitive

---

**SEND APPROPRIATE CULTURES BEFORE PRESCRIBING ANTIBIOTICS**

### Cultures

- [ ] Sent before antibiotics
- [ ] Sent after antibiotics
- [ ] Not sent

*CA = Community acquired within 24h of admission
HA = Hospital acquired >48h after admission or within 30 days of discharge

<table>
<thead>
<tr>
<th>Indication</th>
<th>Medicine Approved Name or GE</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>[P]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[E]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[D]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

### Antibiotic Day

<table>
<thead>
<tr>
<th>Ant. Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
</table>

**Indication**

- [P] Prophylactic
- [E] Empirical
- [D] Definitive

**Dr's Signature & Name**

**Contact**

**Pharmacy**
WAYS TO REDUCE ANTIBIOTIC USAGE IN NEONATOLOGY

- Perform a blood culture prior to start of IV antibiotics
- Stop antibiotics after 48 hours if culture still negative and newborn well
- To not treat for extended periods of time
- To narrow spectrum antibiotics if culture results allow
- Remove risk factors for infection (indwelling catheters / PICC lines or CVP lines) as soon as feasible
LOW-HANGING FRUIT FOR ANTIBIOTIC STEWARDSHIP IN NEONATOLOGY?

Reduce duration of **empiric therapy**

- Stop antibiotics by 48-72hrs

*Pichichiero 96% BC+ by 48hrs; Garcia-Prats 94% BC+ by 48hrs*

Reduce duration of **definitive Rx**

- 7 days adequate for sepsis/pneumonia

*Engle 2000, Gathwala 2010 (excludes meningitis)*
ACKNOWLEDGEMENTS

• KPA
• Angela Dramowski
• UIPC team
• Department of microbiology
• Neonatal colleagues
Antimicrobial stewardship

Objectives
When you have completed this chapter you should:

- Be aware of the global problem of antimicrobial resistance
- Know how and why antimicrobial resistance develops
- Be familiar with the concept of antimicrobial stewardship
- Know some components of antimicrobial stewardship programmes
- Understand the role of IPC in antimicrobial stewardship programmes.

Antimicrobial resistance

9-1 What is an antimicrobial agent?
Antimicrobial agent is a general term used for drugs, chemicals or other substances that kill or slow down the growth of micro-organisms. Antimicrobial agents include antibacterial, antiviral, antifungal, antiparasitic drugs, disinfectants and antiseptic solutions.

An antimicrobial is a substance that kills or slows down the growth of pathogenic micro-organisms.

9-2 What is antimicrobial resistance?
Antimicrobial resistance is the ability of micro-organisms to grow in the presence of a chemical or drug that would normally kill them or slow their growth.

Antimicrobial resistance is the ability of pathogens to grow in the presence of a drug or chemical that would normally kill them or slow their growth.

9-3 What is the impact of antimicrobial resistance?
Antimicrobial resistance makes it more difficult to treat infections because the available drugs become less effective. There are many examples of old infectious diseases which have become more difficult to treat than in the past, e.g. gonorrhoea (a sexually-transmitted disease), malaria and TB (with evolving anti-TB drug resistance).

9-4 Why has antimicrobial resistance developed?
Micro-organisms evolve constantly and are able to survive difficult conditions by adapting to new environments. Factors contributing to the rapid development of antimicrobial resistance.